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Psychiatric disorders during pregnancy in asymptomatic and mildly symptomatic SARS-CoV-2 positive women: Prevalence and effect on outcome

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ABSTRACT

The effect of psychiatric comorbidity on pregnancy outcome among SARS-CoV-2 positive women with asymptomatic and mildly symptomatic infections remains largely unknown. We reviewed the electronic medical records of all pregnant women who received care at Mayo Health System and tested positive for SARS-CoV-2 (RT-PCR) from March 2020 through October 2021. Among 789 patients, 34.2% (n = 270) had psychiatric comorbidity. Of those with psychiatric comrobidity, 62.2% (n = 168) had depression prior to pregnancy, and 5.2% (n = 14) reported new-onset depression during pregnancy. Before pregnancy, 65.6% (n = 177) had anxiety, and 4.4% (n = 12) developed anxiety during pregnancy Thirteen percent of SARS-CoV-2 positive pregnant women (n = 108) received psychotropic medication during pregnancy. In addition, 6.7% (n = 18) and 10.7% (n = 29) of pregnant women with psychiatric comorbidity had documented nicotine, cannabis and/ or illicit substance use during and prior to pregnancy, respectively. We depicted a significantly higher risk for cesarean delivery [35.6% vs. 24.9%) in asymptomatic and mildly symptomatic SARS-CoV-2 positive pregnant women with psychiatric comorbidity. In conclusion, the prevalence rates of depression, anxiety, and prescribed antidepressant medications during pregnancy among asymptomatic and mildly symptomatic SARS-CoV-2 infected women were substantially higher than average, which negatively impacted pregnancy and neonatal outcomes.

1. Introduction

A large number of pregnant women encounter Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV-2) infection. Fortunately, most of these patients experience only mild symptoms or remain asymptomatic (Tanacan et al., 2020; Cardona-Perez et al., 2021; Hill et al., 2021; Ma et al., 2021). Nonetheless, being pregnant during the Coronavirus Disease 2019 (COVID-19) pandemic, regardless of testing positive for SARS-CoV-2 could be stressful (Iyengar et al., 2021; Ashby et al., 2022). At the beginning of the pandemic (April 2020), an online survey of 2740 pregnant women revealed that more than half of them reported heightened stress about food running out, losing a job or household income, or getting infected with COVID-19 (Moyer et al., 2020). Indeed, the prevalence of depression and anxiety increased robustly during the pandemic in pregnant women. In a meta-analysis of 21 studies (n = 19,284 patients), the prevalence of depression before the pandemic was 7.4% in the first trimester, 12.8% in the second trimester, and 12.0% in the third trimester (Bennett et al., 2004), while a recent meta-analysis of 64 studies (n = 95,326) reported 31.4% overall prevalence of depression among pregnant women during the COVID-19 pandemic (Adrianto et al., 2022). Other meta-analyses reported high pooled prevalence for depression and anxiety in western countries of

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25.1% and 38%, respectively. (Ghazanfarpour et al., 2021) and 25.6% and 30.5%, respectively, in another meta-analysis (Tomfohr-Madsen et al., 2021). This marked increase in mental disorders during pregnancy, without a concomitant risk of SARS-CoV-2 infection, is associated with a higher risk of adverse perinatal outcomes such as preterm birth (Grote et al., 2010; Grigoriadis et al., 2013; Ding et al., 2014; Szegda et al., 2014; Jarde et al., 2016; Grigoriadis et al., 2018), cesarean delivery (Rusner et al., 2016; Sanni et al., 2022; Chung et al., 2001; Bayrampour et al., 2015; Nasreen et al., 2019), low birth weight (Field et al., 2006; Grote et al., 2010; Ding et al., 2014; Szegda et al., 2014), smaller head circumference (Grigoriadis et al., 2018), and congenital anomalies (Rusner et al., 2016; Scrandis 2017). Therefore, this increase in mental disorders in pregnant women during the COVID-19 pandemic is concerning. The mental disorder may be attributed to external social factors during the stressful pandemic period, or it may be a neurobiological effect of the COVID-19 infection.

Several studies suggest that asymptomatic SARS-CoV-2 positive pregnant women are at higher risk for an adverse pregnancy outcome compared to non-infected women. Villar et al. reported that asymptomatic SARS-CoV-2 women had a significantly higher risk for maternal morbidity (Relative Risk (RR), 1.24; 95% CI, 1.00–1.54) and pre-eclampsia (RR, 1.63; 95% CI, 1.01–2.63) compared to pregnant women without COVID-19 diagnosis (Villar et al., 2021). In a study of 675 women admitted for delivery, cesarean birth rates were significantly higher among asymptomatic SARS-CoV-2 positive women (n = 55) compared to SARS-CoV-2 negative controls (n = 605) (45.5% vs. 30.9%). Indications for cesarean delivery in asymptomatic SARS-CoV-2 positive pregnant women (vs. controls) were nonreassuring fetal status (5.5% vs. 3.8%), labor indications (12.7% vs. 5.5%), scheduled repeat (10.9% vs. 12.2%), multiple gestation (3.6% vs. 1.8%), malpresentation (1.8% vs. 2.1%), and others (10.9% vs. 2.1%) (Prabhu et al., 2020). This high rate of cesarean deliveries was also reported in a cohort of asymptomatic SARS-CoV-2 positive pregnant women (n = 724) from the United Kingdom (adjusted OR = 2.02, 95% CI, 1.52–2.70) (Vousden et al., 2021). Also, higher rates of premature rupture of membranes were observed among 174 asymptomatic SARS-CoV-2 positive pregnancies at time of delivery compared with 430 SARS-CoV-2 negative pregnancies (asymptomatic SARS-CoV-2 positive pregnancies vs. SARS-CoV-2 negative pregnancies: 17.8% (n = 31/174) vs 10.2% (44/430), P = 0.011, adjusted OR = 1.88, 95% CI, 1.13–3.11) (Cruz-Lemini et al., 2021). on the other hand, several studies reported no differences in outcome between asymptomatic and non-infected women. Saviron-Cornudella et al. identified 65 SARS-CoV-2 positive women among a cohort of 1211 pregnant women (43 with previous exposure, 20 asymptomatic, and 2 mildly symptomatic) and did not find significant differences in maternal or perinatal outcomes among the three studied groups (Saviron-Cornudella et al., 2021). A study from Denmark on 418 SARS-CoV-2 positive pregnant women, of whom 23 required hospitalization for COVID-19, found no differences in any obstetrical or neonatal outcome between SARS-CoV-2 positive and negative women (Aabakke et al., 2021). Similarly, Cosma et al. reported that asymptomatic or mildly symptomatic women during the first trimester of pregnancy (n = 17) did not experience significantly more adverse events than SARS-CoV-2-negative women (n = 164) (Cosma et al., 2022). Another study of 317 SARS-CoV-2 antibody or PCR positive women, in which 217 (68.5%) were asymptomatic and 93 (29.3%) had mild symptoms, found no difference in adverse events between asymptomatic and SARS-CoV-2 negative women (Crovetto et al., 2021). Similarly, a recent small study found no significant differences in fetal growth or preterm delivery between asymptomatic SARs-CoV-2 positive (n = 34) and SARS-CoV-2 negative pregnancies (n = 26) (Bonmati-Santane et al., 2022). Based on these previous studies, the effects of asymptomatic or mild SARS-CoV-2 infection on pregnant women seem to be conflicting or equivocal.

Moreover, there has been no previously published investigation into the impact of co-morbid mental health disorders in pregnant women with mild SARS-CoV-2 infection. A SARS-CoV-2 infection, even mild, could, in theory increase the risk of a psychiatric diagnosis or psychotropic medication use during pregnancy due to immune activation (Bonfante et al., 2021; Petrara et al., 2021). Several studies have already examined the effect of SARS-CoV-2 infection on maternal and fetal outcomes (Adhikari et al., 2020; Ahlberg et al., 2020; Khalil et al., 2020; Angelidou et al., 2021; Chinn et al., 2021; Dumitriu et al., 2021; Handley et al., 2021; Norman et al., 2021).

It is also shown that psychiatric comorbidities could adversely affect pregnant women and neonates (Chung et al., 2001; Wisner et al., 2013; Ding et al., 2014; Bayrampour et al., 2015; Jarde et al., 2016; Grigoriadis et al., 2018; Nasreen et al., 2019; Sanni et al., 2022). The previous studies raise the issue of the role of psychiatric disorders, comorbid with SARS-CoV-2 infection, during pregnancy as a potential confounding factor for the negative maternal and neonatal outcomes. The current study aimed to assess the prevalence of psychiatric comorbidity in pregnant women with SARS-CoV-2 infection and its effect on pregnancy outcomes.

2. Methods

2.1. Patients and data collection

This study was approved by the Institutional Review Board of the Mayo Clinic and the COVID-19 Research Task Force (ID: 21–010,940). It included all pregnant women who received medical care in the Mayo Clinic Health System (MCHS) from March 1, 2020, through October 1, 2021 with confirmed positive SARS-CoV-2 by reverse-transcriptase polymerase chain reaction (RT-PCR) test (nasopharyngeal/oropharyngeal swab specimen). The MCHS is a network of community hospitals across southern Minnesota and western Wisconsin. The last delivery date was March 21, 2022. Patient data included demographics, the COVID-19 symptom check list, the date of the SARS-CoV-2 positive test, the date of delivery, the fetal gestational age at the time of delivery, the delivery method, medical comorbidities during pregnancy or labor, psychiatric diagnoses (depression, anxiety, or substance use) before or during pregnancy and any psychotropic medications during pregnancy. Neonatal outcomes (birth head circumference, weight, and APGAR scores at 1 and 5 min, congenital anomalies, neonatal intensive care unit (NICU) admission, hyperbilirubemia, hyperglycemia, hearing screen result, respiratory symptoms, or fetal demise) were also collected.

2.2. Statistical analysis

Continuous variables were summarized using means (SD) and categorical variables using frequencies and percentages. Individual student t-tests were used to compare the means of continuous variables and Fisher exact analyses were used to compare the frequencies of categorical variables between the two study groups. Binary regression analysis was utilized to examine the effects of psychiatric comorbidities, maternal age, and BMI on the probability of cesarean delivery. Since the timing of in-utero viral infections (Sweeney 1999; Almond and Mazumder 2005) including SARS-CoV-2 (Getahun et al., 2022) and psychiatric comorbidities during pregnancy (Field et al., 2006; Grote et al., 2010; Ding et al., 2014; Szegda et al., 2014; Rusner et al., 2016; Scrandis 2017; Grigoriadis et al., 2018) may affect fetal development differentially, we used the revised Fenton growth chart for preterm infants to calculate the Z-Scores for head circumference and birth weight based on sex and gestational age (Fenton and Kim 2013). We also performed factorial ANOVAs to explore the effects of psychiatric comorbidity and infection timing on neonatal head circumference and on birth weight z-scores covarying for maternal age (years) and BMI. Analyses were performed with PRISM GraphPad 9 (San Diego, CA) and SPSS V28 software (Armonk, NY: IBM Corp). Results are considered significant at $P < 0.05$.

3. Results

3.1. Sample identification

Data from 1021 subjects was identified based on SARS-CoV-2 positive RT-PCR and pregnancy status. A total of 232 records were excluded for having a SARS-CoV-2 positive test before pregnancy or after delivery ($n = 173$), a negative SARS-CoV-2 confirmatory test ($n = 54$), severe COVID-19 infection requiring hospitalization ($n = 3$), or no pregnancy during the study interval ($n = 2$). The final cohort consisted of 789 subjects with SARS-CoV-2 positive tests, 270 with and 519 without psychiatric comorbidities, which were defined as the presence of any documented psychiatric diagnosis or substance use, other than social alcohol drinking, prior to or during pregnancy. Thirty-eight patients (11 with and 27 without psychiatric comorbidity) delivered outside the Mayo Clinic, so the delivery records were missing. We have full records for 731 newborns [First trimester infection ($n = 164$), second ($n = 190$), and third ($n = 377$)]. A total of 481 babies were born to mothers without psychiatric comorbidity: [First trimester infection ($n = 101$), second ($n = 120$), and third ($n = 260$)]. The other 250 infants were born to mothers with psychiatric comorbidity: [First trimester infection ($n = 63$), second ($n = 70$), and third ($n = 117$)]. Fifteen newborns were missing head circumference data.

3.2. Maternal demographics

Compared to the non-psychiatric comorbidity group, pregnant women with psychiatric comorbidity were younger (less than 25 years old: 25.9% vs. 16.0%, $P = 0.001$), white (87.0% vs. 77.3%, $P = 0.0009$), single (40.7% vs. 27.4%), and had fewer years of education (no high school: 17.0% vs. 5.6%, $P<0.0001$). Most patients in both groups were non-Hispanic (86.3% vs. 84.2%, $P = 0.4$) and employed (72.2% vs. 74.8%, $P = 0.4$). See Table 1 for more details.

3.3. Distribution of SARS-CoV-2 positive test and COVID-19 symptoms

Almost half of all infections were recorded in the winter months of November 2020 (percentage of positive tests in patients with and without psychiatric comorbidities: 20.7% and 23.9% respectively), December 2020 (15.6% and 10.8%), and January 2021 (8.1% each). Another peak was observed in August (11.5% and 6%) and September 2021 (7.4% and 9.4%). All cases were reported before the first case of the Omicron variant in the United States in November 2021 (Baker et al., 2022) (Fig. 1).

The vast majority of infected mothers did not report any symptoms. Among those with mild symptoms, we observed a small but significant increase in reported diarrhea in the psychiatric comorbidity group (4.4% vs. 1.5%, $P = 0.017$) (Table 2).

3.4. Comorbid psychiatric conditions and medication

Among patients with comorbid psychiatric conditions ($n = 270$), 62.2% ($n = 168/270$) had depression prior to pregnancy and 5.2% ($n = 14/270$) reported new onset depression during pregnancy. Prior to pregnancy, an anxiety diagnosis existed in 65.6% ($n = 177/270$), while new-onset anxiety existed in 4.4% ($n = 12/270$). Thirteen percent of all pregnant women ($n = 108/789$) were prescribed psychotropic medication. Among the SARS-CoV-2 positive pregnant women with comorbid psychiatric conditions, 40% ($n = 108/270$) received psychotropic medication during pregnancy. The most commonly prescribed antidepressant or antianxiety medication was sertraline in 18.5% ($n = 50/270$) of patients. In addition, 6.7% ($n = 18/270$) of pregnant women with psychiatric comorbidity had documented drug use during pregnancy. Most common drugs were nicotine only (3.0%, $n = 8/270$), and cannabis only (1.1%, $n = 3/270$), and nicotine and/or cannabis in combination with other substances (1.5%, $n = 4/270$). Cannabis or illicit drug use prior to pregnancy was reported in 10.7% ($n = 29/270$) of patients (Table 3).

Table 1
Demographics.

		SARS-CoV-2 Positive ($n = 789$)		Fishe exact test
		With Psychiatric Comorbidity ($n = 270$)	Without Psychiatric Comorbidity ($n = 519$)	
Age at time of delivary	<25	70 (25.9%)	83 (16.0%)	$P = 0.001$
	25–35	163 (60.4%)	323 (62.2%)	$P = 0.6$
	>35	32 (11.9%)	96 (18.5%)	$P = 0.019$
Race	American Indian or Alaska Native	3 (1.1%)	3 (0.6%)	$P = 0.4$
	Asian	1 (0.4%)	24 (4.6%)	$P = 0.001$
	Black or African Americans	9 (3.3%)	38 (7.3%)	$P = 0.026$
	Native Hawaiian or Other Pacific Islander.	0 (0.0%)	0 (0.0%)	$P = 0.9$
	White	235 (87.0%)	401 (77.3%)	$P = 0.0009$
	Other or missing	22 (8.1%)	53 (10.2%)	$P = 0.3$
Ethnicity	Hispanic	32 (11.9%)	74 (14.3%)	$P = 0.3$
	Non-Hispanic	233 (86.3%)	437 (84.2%)	$P = 0.4$
	Missing	5 (1.9%)	8 (1.5%)	$P = 0.7$
Marital status	Single	110 (40.7%)	142 (27.4%)	$P = 0.0002$
	Married	149 (55.2%)	360 (69.4%)	$P = 0.0001$
	Other or missing	11 (4.1%)	17 (3.3%)	$P = 0.5$
Educational level	No high school	46 (17.0%)	29 (5.6%)	$P<0.0001$
	High school	56 (20.7%)	82 (15.8%)	$P = 0.08$
	College (associate or bachelor)	123 (45.6%)	246 (47.4%)	$P = 0.6$
	Advanced degree (MS, MD, PhD, etc.)	18 (6.7%)	51 (9.8%)	$P = 0.14$
	Missing	27 (10.0%)	111 (21.4%)	$P<0.0001$
Employment status	Unemployed	64 (23.7%)	121 (23.3%)	$P = 0.9$
	Employed (full time, or part time)	195 (72.2%)	388 (74.8%)	$P = 0.4$
	Student	6 (2.2%)	8 (1.5%)	$P = 0.5$
	Missing	5 (1.9%)	2 (0.4%)	$P = 0.3$

Age at SARS-CoV-2 positive test for those who are missing delivery date in the psychiatric comorbidity group [33.9 ± 3.9, $n = 5$] and no psychiatric comorbidity group [31.8 ± 5.6, $n = 17$] $t = 0.7756$, df=20, $P = 0.6$.

3.5. Obstetrical history and pregnancy characterization

Compared with the non-psychiatric comorbidity group, patients with psychiatric comorbidity were younger, which is statistically but not clinically significant (28.8 ± 5.2 vs 30.2 ± 5.3 years, $P = 0.0004$). Additionally, patients with psychiatric comorbidity were more likely to have had one full-term birth prior to this pregnancy (38.1% vs. 29.3%, $P = 0.012$) and had more frequent class 3 obesity (BMI >40 Kg/m^2) (20.0% vs. 11.8%, $P = 0.002$). Patients without psychiatric comorbidity had 3 or more full-term births, not including the current pregnancy (19.5% vs. 10.4%, $P = 0.001$), and slightly more frequent gestational diabetes (15.2% vs. 10.0%, $P = 0.047$). No significant differences were observed in obstetrical history of preterm birth, number of abortions, hypertension, preeclampsia, or other medical comorbidities (Table 4).

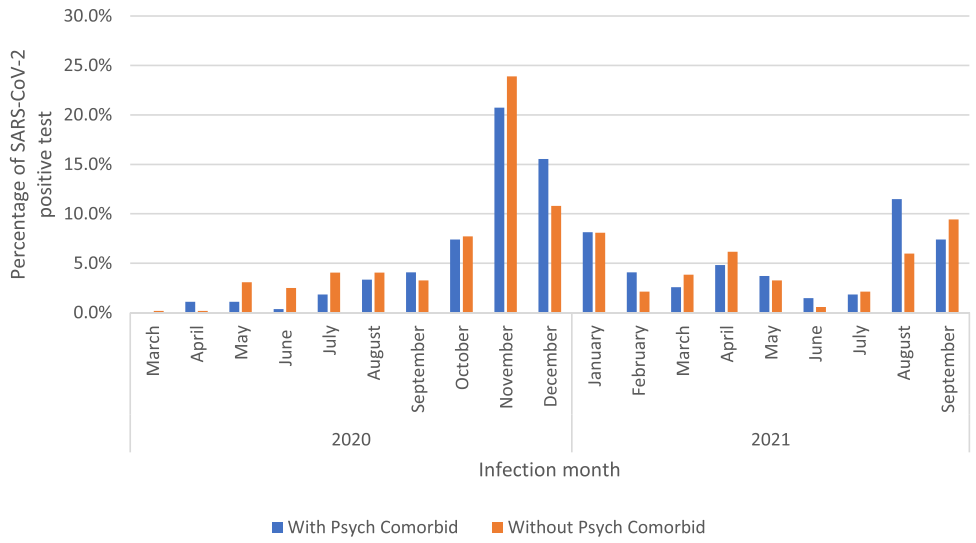

Fig. 1. Distribution of SARS-CoV-2 positive test in patients with and without psychiatric comorbidity.

Table 2
COVID-19 symptom check list.

	SARS-CoV-2 Positive (n = 789)		Fisher exact test
	With Psychiatric Comorbidity (n = 270)	Without Psychiatric Comorbidity (n = 519)	
Chills	7 (2.6%)	10 (1.9%)	P = 0.6
Diarrhea	12 (4.4%)	8 (1.5%)	P = 0.017
Muscle aches	11 (4.1%)	11 (2.1%)	P = 0.1
New or worse cough or SOB	18 (6.7%)	24 (4.6%)	P = 0.2
Fever	8 (3.0%)	15 (2.9%)	P>0.99
Loss of smell	14 (5.2%)	15 (2.9%)	P = 0.11
Loss or change of taste	11 (4.1%)	13 (2.5%)	P = 0.2
Respiratory distress	4 (1.5%)	3 (0.6%)	P = 0.2
Sore throat	7 (2.6%)	8 (1.5%)	P = 0.4
Missing	28 (10.3%)	63 (13.8%)	P = 0.7

Table 3
Comorbid psychiatric conditions.

Depression or other mood disorders	Any mood disorders	182 (67.4%)
	Onset before pregnancy	168 (62.2%)
	Onset during pregnancy	14 (5.2%)
Anxiety disorders	Any anxiety disorders	189 (70.0%)
	Onset before pregnancy	177 (65.6%)
	Onset during pregnancy	12 (4.4%)
Receiving psychotropic medications during pregnancy	Any medications	108 (40.0%)
	Sertraline	50 (18.5%)
	Escitalopram	19 (7.0%)
	Citalopram	10 (3.7%)
	Fluoxetine	10 (3.7%)
	Duloxetine	5 (1.9%)
	Buspirone	5 (1.9%)
	Bupropion or Bupropion XL	4 (1.5%)
	Venlafaxine or desvenlafaxine	4 (1.5%)
	Paroxetine	1 (0.4%)
	Combination*	12 (4.4%)
Drug use during pregnancy	Any drug use	18 (6.7%)
	Nicotine	8 (3.0%)
	Cannabis	3 (1.1%)
	Cannabis + Nicotine	2 (0.7%)
	Cannabis + METH	1 (0.4%)
	Cannabis + Ketamine	1 (0.4%)
	Alcohol	1 (0.4%)
	METH	2 (0.7%)
Drug use prior to pregnancy	Any drug use	29 (10.7%)
	Nicotine	7 (2.6%)
	Cannabis	12 (4.4%)
	Cannabis + Nicotine	1 (0.4%)
	Cannabis + METH	2 (0.7%)
	Cannabis + Ketamine	0 (0.0%)
	Alcohol	2 (0.7%)
	METH	0 (0.0%)
	Stimulant + Synthetic marijuana	1 (0.4%)
	Opioid	1 (0.4%)
	Not mentioned	3 (1.1%)

*Combination with buspirone (n = 5), Lorazepam, alprazolam or Klonopin(n = 3), lamotrigine (n = 2, Abilify (n = 1), or bupropion (n = 1).

3.6. Labor and delivery

The mean gestational age at delivery was not significantly different between the two groups (38.5 ± 1.9 vs. 38.7 ± 1.7 weeks, P = 0.1). Preterm birth (<37 weeks) was documented in 8.1% and 8.9% of patients with and without psychiatric comorbidity, respectively. Asymptomatic and mildly symptomatic SARS-CoV-2 positive pregnant women with psychiatric comorbidity had significantly higher risk for cesarean delivery (35.6% vs. 24.9%, β = 0.520, OR = 1.681, 95% CI (1.190–2.375). The percentage of patients who had cesarean delivery for fetal indications did not differ between the two groups [35.7% (34/95) in patients with psychiatric comorbidity compared to 37.5% (48/95) in patients without psychiatric comorbidity]. In addition, the frequency of meconium-stained amniotic fluid was significantly higher in patients with psychiatric comorbidity (6.3% vs. 1.7%, P = 0.001), (Table 5).

3.7. Neonatal outcomes

More neonates born to asymptomatic or mildly symptomatic SARS-CoV-2 positive mothers with psychiatric comorbidity had hyperbilirubinemia (6.9% vs. 3.0%, P = 0.019). All other parameters including APGAR scores, neonatal hypoglycemia, passing hearing screening test, frequency of congenital anomalies, the presence of respiratory distress requiring neonatal intensive care unit (NICU)

Table 4
Obstetrical history.

		SARS-CoV-2 Positive ($n = 789$)		Student *t*-test or Fisher exact test
		With Psychiatric Comorbidity ($n = 270$)	Without Psychiatric Comorbidity ($n = 519$)	
Maternal age at time of delivery		28.8 ± 5.2	30.2 ± 5.3	$t = 3.584$, df=765, $P = 0.0004$
Number of pregnancies	Primigravida (1st pregnancy)	66 (24.4%)	126 (24.3%)	$P>0.99$
	Multigravida (2–4 pregnancies)	165 (61.1%)	287 (55.3%)	$P = 0.1$
	grand multigravida (≥ 5 pregnancies)	28 (10.4%)	79 (15.2%)	$P = 0.06$
	Missing data	11 (4.1%)	27 (5.2%)	$P = 0.5$
Number of full-term birth(s)	0	72 (26.7%)	125 (24.1%)	$P = 0.4$
	1	103 (38.1%)	152 (29.3%)	$P = 0.012$
	2	56 (20.7%)	114 (22.0%)	$P = 0.7$
	≥ 3	28 (10.4%)	101 (19.5%)	$P = 0.001$
	Missing data	11 (4.1%)	27 (5.2%)	$P = 0.5$
History of preterm labor		27 (10.0%)	60 (11.6%)	$P = 0.5$
Number of previous abortion(s)	0	163 (60.4%)	325 (62.6%)	$P = 0.5$
	1	62 (23.0%)	111 (21.4%)	$P = 0.6$
	2	25 (9.3%)	37 (7.1%)	$P = 0.3$
	≥ 3	9 (3.3%)	19 (3.7%)	$P>0.99$
	Missing data	11 (4.1%)	27 (5.2%)	$P = 0.5$
Number of living children	0	67 (24.8%)	114 (22.0%)	$P = 0.3$
	1	97 (35.9%)	150 (28.9%)	$P = 0.052$
	2	57 (21.1%)	118 (22.7%)	$P = 0.6$
	≥ 3	38 (14.1%)	110 (21.2%)	$P = 0.016$
	Missing data	11 (4.1%)	27 (5.2%)	$P = 0.5$
Medical history	BMI < 30 Kg/m^2	99 (36.7%)	192 (37.0%)	$P = 0.9$
	BMI 30–40 Kg/m^2	116 (43.0%)	257 (49.5%)	$P = 0.08$
	BMI >40 Kg/m^2	54 (20.0%)	61 (11.8%)	$P = 0.002$
	Gestational diabetes	27 (10.0%)	79 (15.2%)	$P = 0.047$
	Hypothyroidism	18 (6.7%)	27 (5.2%)	$P = 0.4$
	Hypertension	35 (13.0%)	65 (12.5%)	$P = 0.9$
	Preeclampsia	15 (5.6%)	36 (6.9%)	$P = 0.5$
	Anemia	24 (8.9%)	66 (12.7%)	$P = 0.12$
	Asthma	23 (8.5%)	37 (7.1%)	$P = 0.3$
	Group β Streptoccocal infection	40 (14.8%)	81 (15.6%)	$P = 0.8$

Table 5
Labor data.

		SARS-CoV-2 Positive ($n = 789$)		Student *t*-test or Fisher exact test
		With Psychiatric Comorbidity ($n = 270$)	Without Psychiatric Comorbidity ($n = 519$)	
Gestational age at time of delivery (weeks)		38.5 ± 1.9	38.7 ± 1.7	$t = 1.602$, df=761, $P = 0.10$
Preterm labor (<37 weeks)		22 (8.1%)	46 (8.9%)	$P = 0.7$
Induced labor		122 (45.2%)	228 (43.9%)	$P = 0.7$
Epidural anesthesia		163 (60.4%)	305 (58.8%)	$P = 0.7$
Instrumental delivery		8 (3.0%)	13 (2.5%)	$P = 0.8$
Normal vaginal delivery		151 (55.9%)	350 (67.4%)	$P = 0.001$
Cesarean delivery		96 (35.6%)	129 (24.9%)	$P = 0.002$
Maternal complications during labor	Fetal heart rate abnormalities	29 (10.7%)	47 (9.1%)	$P = 0.4$
	Obstructed labor or failure to progress	19 (7.0%)	24 (4.6%)	$P = 0.18$
	Meconium-stained amniotic fluid	17 (6.3%)	9 (1.7%)	$P = 0.001$
	Cord prolapse or nuchal cord	11 (4.1%)	22 (4.2%)	$P>0.99$
	Bleeding	10 (3.7%)	21 (4.0%)	$P>0.99$
	Precipitous labor (< 3hours)	8 (3.0%)	19 (3.7%)	$P = 0.6$
	Premature rupture of membrane	7 (2.6%)	6 (1.2%)	$P = 0.14$
	Retained placenta or manual extraction	5 (1.9%)	9 (1.7%)	$P>0.99$
	Chorioamnionitis	4 (1.5%)	6 (1.2%)	$P = 0.7$
	Prolonged labor (> 20 hr)	4 (1.5%)	5 (1.0%)	$P = 0.5$
	Group β Streptoccocal infection	3 (1.1%)	9 (1.7%)	$P = 0.7$

admission, or fetal demise, did not differ between the psychiatric and non-psychiatric comorbidity groups (Table 6).

3.8. Effect for comorbid psychiatric conditions or SARS-CoV-2 infection timing on neonatal head circumference and birth weight

We found no significant effect of gestational trimester timing of SARS-CoV-2 infection or comorbid psychiatric conditions on head

Table 6
Neonatal data.

		SARS-CoV-2 Positive mothers (n = 789)		Fisher exact test
		Neonates born to mothers with Psychiatric Comorbidity (n = 248)	Neonates born to mothers without Psychiatric Comorbidity (n = 468)	
Apgar Score ≤3	at 1 min	8 (3.2%)	13 (2.8%)	$P = 0.8$
	at 5 min	3 (1.2%)	4 (0.9%)	$P = 0.6$
Hyperbilirubinemia		17 (6.9%)	14 (3.0%)	$P = 0.019$
Hypoglycemia		6 (2.4%)	14 (3.0%)	$P = 0.8$
Did not pass hearing screening		3 (1.2%)	4 (0.9%)	$P = 0.6$
Congenital anomalies	All	8 (3.2%)	11 (2.4%)	$P = 0.4$
	Genitourinary (congenital hydronephrosis, congenital hydronephrosis, undescended testis, hypospadias, penile torsion, inguinal hernia)	4 (1.6%)	4 (0.9%)	$P = 0.4$
	Cardiovascular (VSD, PDA, heart murmur, pulmonary hypertension, thrombocytopenia)	1 (0.4%)	3 (0.6%)	P>0.99
	Oral cavity (labial and lingual frenulum, tied tongue, cleft palate, ankyloglossia)	2 (0.8%)	1 (0.2%)	$P = 0.2$
	Skin (melanocytosis, sacral dermal melanosis, ear deformity)	0 (0.0%)	3 (0.6%)	$P = 0.5$
	VLCAD (very long chain Acylium Dehydrogenase deficiency)	1 (0.4%)	0 (0.0%)	$P = 0.3$
Respiratory distress requiring NICU admission		9 (3.6%)	15 (3.2%)	$P = 0.8$
Fetal demise		3 (1.2%)	3 (0.6%)	P>0.99

circumference z-scores [trimester effect: F(2, 708)=0.263, $P = 0.7$, psychiatric comorbidities effect: F(2, 708)=0.030, $P = 0.8$] or on body weight z-scores [trimester effect: F(2, 723)=0.774, $P = 0.4$, psychiatric comorbidity effect: F(2, 723)=0.040, $P = 0.8$], using maternal age at time of delivery and BMI as covariates.

4. Discussion

This study showed the very high prevalence of psychiatric comorbidity and antidepressant use during pregnancy. One third of pregnant women with asymptomatic or mildly symptomatic SARS-CoV-2 infection in this cohort of 789 patients had comorbid depression, anxiety or substance use and over 13% are prescribed antidepressant medications during pregnancy. Furthermore, patients with comorbid psychiatric disorders had higher risk of cesarean delivery, meconium-stained amniotic fluid, and neonatal hyperbilirubinemia. Equally important, the presence of psychiatric comorbidity in this group of patients was not associated with increased risk for preterm labor, or negative neonatal outcomes specifically birth weight, head circumference, respiratory distress, NICU admission, or fetal demise.

4.1. The prevalence of depression and anxiety and antidepressant use during pregnancy

As many as one-third of all patients in this cohort had a documented diagnosis of either depression or anxiety. Our results are consistent with a recent report of depression (26%) and anxiety (32%) in a cohort of 281 pregnant women with direct or indirect exposure to the SARS-CoV-2 virus in Italy (Grumi et al., 2021) and with recent metaanalyses as well (Ghazanfarpour et al., 2021; Tomfohr-Madsen et al., 2021; Adrianto et al., 2022). It is important here to note that our study specifically examined the prevalence of depression and anxiety among asymptomatic and mildly symptomatic patients while other studies included asymptomatic, symptomatic, and severe cases. It is possible that the stress of being pregnant during the pandemic contributes to the development of new-onset depression (Moyer et al., 2020; Iyengar et al., 2021). Moreover, subclinical viral infections are associated with immune activation (Bonfante et al., 2021; Petrara et al., 2021), which may trigger mood or anxiety symptoms (Maes et al., 2002). However, the incidence of new-onset depression or anxiety in our cohort (about 5% of patients with comorbid psychiatric conditions or 1.6% (13/789) of the whole cohort) was the same incidence (1.6%) reported in a study on 1066 pregnant women before the pandemic (Banti et al., 2011).

Surprisingly, 13.6% of the whole cohort received antidepressant medication during pregnancy. This rate is markedly higher than the percentage of women using antidepressants during pregnancy in the Quebec Pregnancy Cohort (n = 186,165 women) where the prevalence of antidepressant medication use during pregnancy was 4.5% (Berard and Sheehy 2014). Similarly, a large-scale Canadian study of 97,680 pregnant women showed a 3.7% rate of antidepressant use during pregnancy (Ramos et al., 2007) and the rate of antidepressant use was 2% in another study of 29,005 pregnant women in the Netherlands (Ververs et al., 2006). Even during the pre-COVID-19 pandemic period, pregnancy is associated with an increase in antidepressant use. Jimenez-Solem et al. reported a 16-fold increase (from 0.2% to 3.2%) in the rate of antidepressant use during pregnancy between 1997 and 2010 in a cohort study including almost one million (n = 912,322) pregnancies (Jimenez-Solem et al., 2013), and a recent metaanalysis of 40 cohorts from 15 countries (n = 14,072,251 pregnancies) estimated the pooled prevalence of 5.5% in North America (Molenaar et al., 2020). The prevalence of antidepressant use in our cohort (13.6%) is even higher than this most recent report. Unfortunately, our study did not include data on whether this high rate of antidepressant use could also be observed in SARS-CoV-2 negative women. Several factors contribute to the high prevalence of antidepressant use in our patient population. For example, the community mental health services in the upper Midwest, where MCHS is located, are robust compared to the rest of the country and the world. So, our sample maynot be nationally representitive because within the United States, there is State-variation in health care spending, insurance eligibility and payment policies (Grogan 2014) with disparities in quality and care for minorities and individuals in rural or urban settings, and for populations in lower socioeconomic brackets. (McAlister and Helton 2021)"

4.2. The prevalence of substance use disorders during pregnancy

Eighteen and 29 (6.7%, and 10.7%, respectively) patients with psychiatric comorbidity (2.2% and 3.6% of the total cohort respectively) had a documented nicotine, cannabis or illicit drug use during or prior to pregnancy. Nicotine and cannabis were the two most commonly used substances. These results are close to the 2.6% pooled prevalence of tobacco use reported among 58,922 pregnant women from 54 low- and middle-income countries (Caleyachetty et al., 2014). However, our substance use prevalence rate seems to be lower than a recent report by Volkow et al. on cannabis use through self-reported survey data from 4000 pregnant women. The adjusted prevalence of past month cannabis use increased from 3.4% in 2002–2003 to 7.0% in 2016–2017 (Volkow et al., 2019). Similarly, high rates of nicotine and cannabis use

(identified by a urine drug screen) in a recent report of 1197 pregnant women showed 8.3% had positive nicotine metabolites, 3.9% had positive cannabis metabolites and 2.8% had positive nicotine and cannabis in urine samples (Smid et al., 2022). It is important to note here that the laws in the state of Minnesota do not encourage accurate self-reporting of cannabis use because that data will be reported to the state with potential legal ramifications (https://www.house.leg.state.mn.us/SessionDaily/Story/15675).

4.3. Effect of psychiatric comorbidity on cesarean delivery

In our study, patients with psychiatric comorbidity had significantly more cesarean delivery (35.6% vs. 24.9%). Our results are consistent with recent data from the population based FinnBrain Birth Cohort Study ($n = 3619$), which showed that maternal psychological distress increased the likelihood of having an elective cesarean delivery (OR: 1.04, 95% CI 1.01–1.06, $p = 0.003$) (Sanni et al., 2022). In addition, Bayrampour et al. reported that pregnant women with depressive symptoms in the third trimester had a significantly increased risk of emergency cesarean delivery (aOR = 2.04; 95% CO, 1.26–3.29), and those with depressive symptoms in the second trimester had an increased risk of elective cesarean delivery (OR, 1.58; 95%CI, 1.07–2.35) (Bayrampour et al., 2015). Another study of 959 women who were followed longitudinally from early pregnancy to postpartum showed that depression in late pregnancy was associated with an increased likelihood of cesarean delivery (39% vs. 27%, p =0.02) (Chung et al., 2001). Similarly, a study on 799 pregnant women from Malaysia reported that antepartum depression was significantly associated with an increased risk of cesarean delivery (RR = 2.44; 95% CI 1.48–4.03) (Nasreen et al., 2019).

Only 37% of cesarean births in each of the psychiatric and non-psychiatric comorbidity groups were attributed to fetal indications. This finding suggests that the higher incidence of cesarean deliveries among patients with psychiatric comorbidity was elective. Our data does not include the number of previous cesarean deliveries, which could confound the results. However, 19.5% of women without psychiatric comorbidity had three or more full-term births, not including the current pregnancy (vs. 10.4% of patients with psychiatric comorbidity). This does not reflect the number of previous cesarean deliveries. A recent study compared nulliparous women who reported depression during pregnancy ($n = 242$) to nulliparous women who did not report depression during pregnancy ($n = 1081$) and found no association between depression and cesarean delivery (30.5% vs. 29.6%, respectively) (Ayala et al., 2022). Further research is needed to examine the effect of comorbid psychiatric disorders on delivery methods and the potential impact, if any, of the immunological perturbation due to subclinical viral infections such as SARS-CoV-2. (Silasi et al., 2015)

4.4. No effect of psychiatric comorbidity on the incidence of preterm birth

In this study, the frequency of preterm labor (<37 weeks) did not differ between the two groups (with and without psychiatric comorbidity: 8.1% and 8.9%, respectively). According to the 2014 data on U.S. births before the COVID-19 pandemic, preterm deliveries occurred in 7.7% of single-gestation pregnancies (Hamilton et al., 2015). Our rate was very close to recent Swedish data (8.8%) (Norman et al., 2021). One meta-analysis of 42 studies involving 43,548 pregnant women found that COVID-19 was associated with 8.5% overall preterm labor, which was a significant increase in preterm labor compared to non-COVID-19 pregnancies (5.8%, OR 1.82, 95% CI 1.38 to 2.39) (Wei et al., 2021). Other studies also reported similar rates. Blitz et al. reported a preterm labor rate of 8.8% in asymptomatic SARS-CoV-2 infected mothers compared to 7.1% in un-infected mothers and 19% in symptomatic cases (Blitz et al., 2021). A few studies reported no significant differences in preterm labor between asymptomatic SARS-CoV-2 positive ($n = 34$) and SARS-CoV-2 negative pregnancies ($n = 26$) (Bonmati-Santane et al., 2022), or between patients with a confirmed COVID-19 diagnosis ($n = 172$) and COVID-19-negative women ($n = 2299$) (Harel et al., 2021). Depression and anxiety are also known risk factors for preterm labor. In a meta-analysis of 23 studies ($n = 25,663$), untreated depression was associated with significantly increased risks of preterm birth (odds ratio [OR], 1.56; 95% CI, 1.25–1.94; 14) and low birth weight (OR, 1.96; 95% CI, 1.24–3.10) (Jarde et al., 2016). Similarly, Ding et al. reported that maternal anxiety during pregnancy was associated with a significantly increased risk of preterm labor (pooled RR=1.50, 95% CI=1.33–1.70) (Ding et al., 2014). In another meta-analysis, maternal anxiety was associated with increased odds for preterm birth (pooled odds ratio [OR] = 1.54; 95% confidence interval [CI], 1.39 to 1.70) (Grigoriadis et al., 2018). Whether comorbid depression and anxiety in pregnant women with asymptomatic SARS-CoV-2 infection truly increase the risk of preterm labor requires further investigation through large-scale national data sets.

4.5. Effect of psychiatric comorbidity in SARS-CoV-2 positive mother on neonatal hyperbilirubinemia

We found a significantly higher rate of hyperbilirubinemia in neonates born to asymptomatic and mildly symptomatic SARS-CoV-2 positive mothers with psychiatric comorbidity than those without psychiatric comorbidity (6.9% vs. 3.0%, $P = 0.019$). Our relatively small sample size did not allow for assessment of the effect of concomitant SSRI treatment on the incidence of neonatal jaundice. One study examined neonatal outcomes in 997 infants after maternal use of antidepressants and found no increased risk for neonatal jaundice after SSRI treatment (OR: 0.96, 95% CI 0.63–1.46) (Kallen 2004). On the other hand, Dumitriu et al. reported that maternal severe or critical SARS-CoV-2 infection was associated with an increased risk of neonatal hyperbilirubinemia requiring phototherapy compared with newborns of mothers with asymptomatic/mild COVID-19 (3 of 10 [30.0%] vs 6 of 91 [7.0%]; $P = 0.04$) (Dumitriu et al., 2021). In contrast, a study from India found no difference in neonatal hyperbilirubinemia between neonates born to SARS-CoV-2 positive women ($n = 92$), when 93.5% of mothers were asymptomatic, and SARS-CoV-2 negative patients ($n = 214$) (Peepal et al., 2022). Given the small number of studies, further research utilizing large data sets is needed to assess the effect of asymptomatic SARS-CoV-2 infection on neonatal hyperbilirubinemia.

4.6. No effect of psychiatric comorbidity and maternal infection timing on birth weight or neonatal head circumference

We did not find a significant effect of infection timing (trimester) during pregnancy or psychiatric comorbidity on neonatal birth weight or head circumference z-scores. Previous reports on the effect of infection timing on neonatal outcomes are also mixed. No trimester effect was found on composite obstetric outcome in a cohort of 1326 pregnant COVID-19 mothers including 103 (8%), 355 (27%) and 868 (65%), who tested positive for SARS-CoV-2 in the first, second, and third trimesters, respectively (Schell et al., 2022). Another study found no significant differences in fetal growth between asymptomatic SARs-CoV-2 positive ($n = 34$) and SARS-CoV-2 negative pregnancies ($n = 26$) (Bonmati--Santane et al., 2022). Similarly, asymptomatic, or mildly symptomatic women during the first trimester of pregnancy ($n = 16$) did not experience significantly more adverse events than SARS-CoV-2-negative women ($n = 105$) (Cosma et al., 2022).

In contrast, one study found that maternal diagnosis of COVID-19 ($n = 586$) carried an increased rate of lower neonatal weight and head circumference at birth compared to neonates born to SARS-CoV-2 negative mothers ($n = 1535$) (Giuliani et al., 2022). Others have reported that maternal SARS-CoV-2 infection increased the odds of congenital anomalies (Getahun et al., 2022) or admission to the neonatal intensive care unit (NICU) (Stephansson et al., 2022). The data on the SARS-CoV-2 infection's effect on fetal growth is equivocal, so there may

be other confounding factors.

Depression and anxiety during pregnancy increase the risk of adverse neonatal outcomes. In a meta-analysis of 12 studies ($n = 17,304$), Ding et al. reported that maternal anxiety during pregnancy was associated with a significantly increased risk of low birth weight (pooled RR=1.76, 95% CI=1.32–2.33) (Ding et al., 2014). In another meta-analysis, maternal anxiety was associated with increased odds for low birth weight (OR = 1.80; 95% CI, 1.48 to 2.18) and a smaller head circumference (mean difference = −0.25 cm; 95% CI, −0.45 to −0.06 cm) (Grigoriadis et al., 2018). Untreated depression was associated with significantly increased risks of low birth weight (OR, 1.96; 95% CI, 1.24–3.10) in a meta-analysis of 23 studies ($n = 25,663$) (Jarde et al., 2016). Importantly, neither antenatal major depression, nor exposure to antidepressants was significantly associated with changes in fetal head circumference relative to nonexposure to either one (Wisner et al., 2013). Taken together, it is evident that there is a complex relationship between SARS-CoV-2 and comorbid psychiatric conditions and their combined impact on pregnancy and neonatal outcomes requires further studies.

5. Limitations

The results of this study should be viewed in light of its limitations, including the retrospective design and relatively small sample size, which prevented subgroup analyses of different SARS-CoV-2 variants (Birol Ilter et al., 2022), the effects of new-onset anxiety and depression, or concurrent SSRIs or substance use on pregnancy outcomes. In addition, the data collection did not include psychotropic medication doses or the extent of substance use. All these factors may confound the results, particularly in patients with heavy substance use. Finally, we did not include a SARS-CoV-2 negative pregnant control group because a negative test or absence of antibodies does not necessarily mean that the individual was not exposed to the infection outside the testing window.

6. Conclusion

The current study brings new insights into the prevalence of psychiatric comorbidities during pregnancy in a cohort of asymptomatic and mildly symptomatic SARS-CoV-2 positive women. We raise the awareness that one out of eight mothers in this community sample is prescribed antidepressant medication during pregnancy. This high prevalence of psychiatric medication use, especially SSRI, during pregnancy in this study is concerning and calls for further investigation.

Author statement

The results in this paper are original and have not been published or under consideration for publication elsewhere and have been approved by all the authors.

Author contributions

Dr Abulseoud have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: OAA. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: OAA. Critical revision of the manuscript for important intellectual content: OAA, BC, EYR and TDS. Administrative, technical, or material support: All authors. Supervision: OAA.

Declaration of Competing Interest

None of the authors report any conflict of interest

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